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Treatment of Pediatric IgA Nephropathy

Keith K. Lau, Lavjay Butani

IgA nephropathy is the most common chronic glomerulopathy in children and young adults. Although most of the early studies on pediatric IgA nephropathy concluded that it was a benign condition, more recent data have shown that a significant proportion of children progress to end-stage renal disease. It is now obvious that IgA nephropathy in children is not as benign as previously thought. Physicians who care for children with IgA nephropathy should be aware of this risk of progression to renal insufficiency and make treatment a priority. Strict attention should be given to modify any coexisting morbidities that may further predispose young patients to renal deterioration. The pharmacologic agents and therapeutic options used to manage this common disease are reviewed, and a recommended approach is presented. [*Hong Kong J Nephrol* 2007;9(2):70–6]

Key words: chronic glomerulopathy, end-stage renal disease, pediatric IgA nephropathy

在兒童及青少年間，IgA 腎病變是最常見的腎小球病變。即使大多數的早期研究指出，兒童期的 IgA 腎病變是一種良性疾病，然而近年的數據顯示，這些病童有不少會演變至末期腎病。因此，目前一般認為，兒童期的 IgA 腎病變並非良性，醫生務須為這些病人提供有效治療，並對其他可能造成病情惡化的因素作出處理，以降低演變至末期腎病疾的風險。本文對此常見腎病的用藥及療程選項作出回顧，並建議一套可行的方案。

Introduction

IgA nephropathy is the most common chronic glomerulopathy in children and young adults [1]. Although most of the early studies on pediatric IgA nephropathy concluded that it was a benign condition [2,3], recent data have shown that a significant proportion of children progress to end-stage renal disease [4–6]. A recent study from Memphis, Tennessee, USA, showed that the predicted 10- and 20-year renal survival rates in Caucasian children with IgA nephropathy were 91% and 80%, respectively [7]. Therefore, it is now obvious that IgA nephropathy in children is not as benign as previously thought. Physicians caring for children with IgA nephropathy need to be aware of this risk of progression to renal insufficiency and make treatment a priority. Moreover, strict attention needs to be given to modify any coexisting morbidities that may further predispose young patients to develop renal deterioration, such as obesity, hypertension and dyslipidemia.

Paucity of Evidence-based Guidelines in Children

As the number of patients with IgA nephropathy in each individual pediatric center is relatively small, there are very few randomized control trials in pediatric patients compared to adults. This is further compounded by the marked differences in the natural history of the disease in children compared to adults. Most pediatric patients with progressive IgA nephropathy have an insidious deterioration in renal function and do not reach end-stage renal disease until adulthood. Therefore, the common outcome measure of progressive renal failure is less applicable in pediatric studies, since few if any children are likely to reach this end point during their pediatric years. Most of the surrogate markers of outcomes that have been used in pediatric studies, such as doubling of serum creatinine and reduction of proteinuria, have not been validated as being meaningful outcome measures, and so the conclusions elucidated from these studies may be

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inappropriate. Notwithstanding these caveats, the small number of pediatric studies that have been performed have contributed to a better understanding of this disease and do provide data that can be useful to the health care provider in managing this common disease.

Pharmacologic Agents in Treatment of Pediatric IgA Nephropathy

The following pharmacologic agents and therapeutic options have been studied in either adults or children.

Corticosteroids

Corticosteroids have been widely used in pediatric patients with moderate to severe IgA nephropathy (characterized by heavy persistent proteinuria, renal insufficiency or hypertension). However, it is quite difficult to draw any conclusion on their effectiveness in the preservation of renal function as there are wide discrepancies in the studies with respect to length of follow-up, doses and routes of steroids used and the use of concomitant medications. Also, some of these studies were uncontrolled, making it difficult to ascertain if the improvements in laboratory or clinical data were related to the intervention or to a part of the natural history of the disease itself [8–20]. There have been two randomized trials on the use of steroids in children to date [10,12]. In the first study, 20 children were enrolled in a crossover trial. Each patient was initially treated with oral prednisone and then switched to placebo after 12 weeks. The efficacy was assessed by using surrogate end points including improvements in microscopic hematuria and proteinuria. Treatment with prednisone failed to show any advantage in that study [10]. However, as most of the children in that study had either normal or mild histologic changes, and the mean protein excretion was around 500 mg/day, they would be at low risk of disease progression and not be likely to merit any therapy in the first place. The other recent randomized study from Japan involved treatment regimens that included prednisone plus azathioprine versus warfarin and dipyridamole [12]. Although the study group demonstrated a significant reduction in proteinuria compared to the control group, the regimens that were used in the study are not popular outside Japan.

Although nephrotic syndrome is not a common presenting feature of children with IgA nephropathy, a subset of patients with IgA nephropathy present with nephrotic syndrome and have minimal change histology on their biopsies; these children do rapidly and completely respond to steroids, similar to children with idiopathic steroid-sensitive nephrotic syndrome. Clive et al reviewed the literature and concluded that other than higher serum IgA levels and a slower response to steroids, patients with nephrotic syndrome and IgA nephropathy with minimal change on biopsy are indistinguishable from other patients with minimal change disease [21]. Since in a study that described 200 consecutive necropsies, 4% of non-IgA nephropathy patients were found to have IgA deposits in their mesangium [22], it is still not clear whether the presence of IgA in the mesangium of patients with minimal change histology represents a true subset of IgA nephropathy or is an incidental finding. Although there is no randomized controlled trial to support this approach, steroids are recommended in pediatric IgA nephropathy patients with nephrotic syndrome [23,24].

Hence, although corticosteroids have been recommended in patients with moderate to severe IgA nephropathy, the recommendations are based on anecdotal studies before the widespread use and availability of angiotensin converting enzyme (ACE) inhibitors. Most pediatric nephrologists would now consider administering steroids only after the failure of ACE inhibitors and/or angiotensin receptor blockers (ARBs), except perhaps in rapidly progressive glomerulonephritis or with severe nephrotic–nephritic syndrome.

Angiotensin blockade

ACE inhibitors have been used in IgA nephropathy to reduce proteinuria by reducing intraglomerular pressure and by improving the permeability characteristics of the glomerular basement membrane [25]. Small-scale prospective studies in adults have also advocated the addition of ARBs for additional benefit [26–29]. The recently published COOPERATE study, in which almost 50% of the patients had IgA nephropathy, showed that compared to monotherapy, a combination of ACE inhibitors and ARBs was more effective in reducing proteinuria and slowing the progression of renal failure [30]. The ongoing ACEARB study is the first multicenter open-label randomized clinical trial to test whether angiotensin blockade would decrease the risk of renal deterioration in patients with IgA nephropathy. Patients 3–60 years old with mild clinical features at onset, including those with normal renal function, normal blood pressure and proteinuria of < 1 g/day are being enrolled. Patients are to be randomized to receive ramipril, irbesartan or supportive therapy and will be followed for 5 years or when the end point of the study (50% increase in proteinuria) is reached [31]. Unless clinically contraindicated, such as in the setting of rapid deterioration of renal function, we are now treating all our patients who have heavy persistent proteinuria with ACE inhibitor and/or ARB irrespective of their blood pressure. Usually, we start patients on a lower dose and then titrate up according to their response. Recent studies also suggest that aldosterone blockade may have a further additive effect in reducing proteinuria and retarding

progression of renal disease [32]. However, until further studies become available, the routine use of aldosterone blockade cannot be recommended in patients with IgA nephropathy, especially considering the risk of hyperkalemia with this combination.

Immunosuppressive medications

A more aggressive approach to the treatment of severe pediatric IgA nephropathy with immunosuppressive medications has been reported by some, although most of the studies related to this were not performed in a large-scale, prospective and randomized fashion.

Azathioprine

Azathioprine combined with oral steroids was evaluated in 10 children with IgA nephropathy [9]. These children had proteinuria of > 1 g/day, elevated blood pressure and renal insufficiency. Treatment consisted of daily oral prednisone (60 mg/m^2/day, maximum 60 mg) with azathioprine (2–3 mg/kg/day) for 8 weeks, followed by alternate day oral prednisone at 60 mg/m^2 for another 10 months. The treated patients showed an improvement in protein excretion. Since these children were not treated with ACE inhibitors, the results suggest that oral steroids and azathioprine may be useful in reducing proteinuria and in a group of children with relatively severe presentation [9]. A randomized trial study from the Japanese Pediatric IgA Nephropathy Treatment Study Group compared the efficacy of a regimen comprised of oral prednisone and azathioprine versus heparin–warfarin and dipyridamole [12]. After 2 years of treatment, there was no difference in mean creatinine clearance between the two groups. However, in the steroid/azathioprine group, there was a significant improvement in proteinuria and no increase in the percentage of glomeruli showing sclerosis upon re-biopsies. Although this study is the largest randomized controlled trial in the treatment of pediatric IgA nephropathy, the treatment regimen that included heparin, warfarin and dipyridamole is not widely used outside Japan. Also, apparently very few of the subjects were treated with ACE inhibitors and the observation of significant reduction in proteinuria in the treatment group might also be achieved with ACE inhibitors. The long-term benefit of prevention of progression to renal failure with this regimen is still unclear.

Mycophenolate mofetil

To date, there are only four prospective randomized controlled trials in adult patients with IgA nephropathy to study the clinical efficacy of mycophenolate mofetil (MMF) [33–36], and the results have been conflicting. The studies from USA and Belgium showed no benefit [17,33], while the studies from Hong Kong and China suggested that MMF treatment had beneficial effects in lowering proteinuria [34,36]. Although the results of using MMF in adults may be encouraging, there are currently no data in children evaluating the efficacy of MMF in IgA nephropathy. The North American IgA Nephropathy Study intended to study the effectiveness of MMF versus placebo in children and adults after 3 months of pretreatment with ACE inhibitors and fish oil. However, the children enrolled in the study all became better after 3 months of ACE inhibitor and fish oil, and no longer qualified for the study [37]. An evidence-based recommendation for the use of MMF in pediatric patients, therefore, cannot be made at the present moment.

Cyclophosphamide

Although early reports [38–40] showed conflicting results on the capability of cyclophosphamide to slow the progression of renal function deterioration, a recent randomized trial from the United Kingdom has suggested that cyclophosphamide may be beneficial in patients with IgA nephropathy and renal insufficiency [41]. The study consisted of 38 IgA nephropathy patients with hypertension and renal insufficiency (serum creatinine > 1.5 mg/dL). None of the patients was given an ARB for blood pressure control. The treatment group received oral prednisone and cyclophosphamide followed by azathioprine while the control group did not receive any immunosuppressant. The treatment group had significantly better renal outcome compared to the controls. Renal survival rates at 5 years were 72% and 6% in the treatment and control groups, respectively. Similar data in children are lacking, making it difficult to justify the use of such a potentially toxic agent in pediatric patients except in high-risk situations.

Cyclosporin

In a randomized prospective single blind study from Hong Kong, 19 Chinese adults with proteinuria of > 1. 5 g/day were randomized to receive either cyclosporin (5 mg/kg/day) or placebo [42]. Although the treatment group had a significant reduction in proteinuria, the authors observed an increase in serum creatinine and reduction in glomerular filtration rate in the treatment group even though the plasma cyclosporin levels were maintained in a very tight range. The therapeutic role of cyclosporin in the treatment of IgA nephropathy is still unknown.

Leflunomide

A recent randomized study in adults with IgA nephropathy compared the efficacy of leflunomide with fosinopril [43]. The leflunomide treated group showed a significant decrease in proteinuria, but this was comparable to the group treated solely with fosinopril. Based on the current data, we are not able to recommend the usage of leflunomide in children with IgA nephropathy [43].

Fish oil

Donadio et al, in an elegant randomized controlled trial, demonstrated that treatment with fish oil in adults with IgA nephropathy delayed the rate of renal function deterioration [44]. The study did include a few pediatric patients. However, a recent meta-analysis of all published studies up to 1997 concluded that fish oil is of minimal benefit [45]. Moreover, in a recent randomized trial of alternate day prednisone or daily omega-3 fatty acids in children and young adults with IgA nephropathy, children treated with fish oil failed to show benefit over placebo in slowing disease progression [46]. Although the data on the beneficial effect of fish oil on retarding disease progression in IgA nephropathy are conflicting, some authors do use it, since it is very safe, with minimal side effects. Until more data is available however, especially in children, fish oil is not recommended as a routine treatment in pediatric patients with IgA nephropathy.

Vitamin E

In a randomized, double-blinded study in children with very mild but biopsy-proven IgA nephropathy, patients treated with vitamin E had significant reduction of proteinuria [47]. Children in the study who were treated with vitamin E had a reduction in their urine protein to creatinine ratio (mg/mg) from 0.31 to 0.24 at 1 year, while the urine protein to creatinine ratio in the control group increased from 0.52 to 0.64. Although the authors suggest that vitamin E could be useful in reducing proteinuria, long-term follow-up is needed to determine its efficacy in the preservation of renal function, especially in patients who are more likely to benefit from any intervention, i.e. those with more severe disease.

Anti-clotting agents

Warfarin and dipyridamole have been used for a long time in Japan for the treatment of IgA nephropathy. Yoshikawa and Ito demonstrated that after 2 years of combined therapy with prednisolone, azathioprine, heparin, warfarin and dipyridamole, patients showed better outcome compared to those randomized to heparin–warfarin and dipyridamole therapy [48]. Also, the treatment group had reduced immunologic renal injury and less sclerosed glomeruli, which suggested a benefit in slowing the progression of renal deterioration. Urokinase has also been used in the treatment of IgA nephropathy in non-randomized trials [49–51]. A recent study from China showed beneficial effects of monthly intravenous urokinase for 10 days [52]. Combined with benazepril, the authors demonstrated that the regimen was more effective in reducing proteinuria and slowing renal deterioration than benazepril alone. Hence, warfarin, dipyridamole and urokinase have all been used either alone or in combination with other agents in the treatment of IgA nephropathy with beneficial effects; however, there are still insufficient data to recommend the routine usage of such agents in clinical practice.

Tonsillectomy

Most of the data promoting tonsillectomy are from adult studies. A recent study of 70 adult patients by Sato et al, who used doubling of serum creatinine as a surrogate marker of poor renal outcome, provided evidence on the efficacy of tonsillectomy [53]. The study included adult patients with moderate IgA nephropathy with serum creatinine > 1.5 mg/dL. Patients were divided into three treatment groups: steroids plus tonsillectomy, steroids alone, and supportive therapy only. Doubling of serum creatinine occurred in 16% of patients in the steroid plus tonsillectomy group compared to 64% in the steroid group and 73% in the supportive group. In another retrospective study in Japan with 118 patients who were followed for over 20 years [54], renal survival in patients with or without prior tonsillectomy was 90% and 64%, respectively. Also, in a recent prospective randomized study by Kawasaki et al, the efficacy of tonsillectomy was studied in 32 Japanese children [55]. Sixteen children who received tonsillectomy and pulse steroids were compared to another 16 children who were treated with oral steroids, warfarin, dipyridamole and mizoribine (PWDM). There were no untreated controls in the study. The authors concluded that tonsillectomy plus pulse steroids are as effective as the PWDM regimen in controlling proteinuria, and able to prevent flares of IgA nephropathy from tonsillitis.

It is obvious that a study that involves a surgical procedure such as tonsillectomy cannot be blinded, and the treatment protocols employed in these studies are not widely used in other parts of the world. At present, there are insufficient data to recommend tonsillectomy as a safe and viable treatment option for children with IgA nephropathy.

Recommended Approach

Since there is no specific treatment for patients with IgA nephropathy, the primary goal of management is to preserve renal function and slow down renal deterioration.

The Figure depicts an algorithm that we are currently using in our center for children with IgA nephropathy. However, we state that the current treatment of IgA nephropathy in pediatric patients is not guided by results of well-designed pediatric randomized controlled trials that employed appropriate outcome measures, but on data extrapolated from adult studies.

Although we do not recommend any specific treatment for pediatric patients with clinically mild IgA nephropathy, we do recommend controlling all other potential risk factors for disease progression such as hypertension. In one of our previous institutions, 30% of children with biopsy-proven IgA nephropathy had elevated blood pressure at presentation [56]. The first-line medications that we use to treat hypertension in this setting are ACE inhibitors and/or ARBs. Patients with mild IgA nephropathy who have normal blood pressure, normal renal function, and only low-grade proteinuria (urine protein to creatinine ratio < 1.0) need no treatment. Similarly, recurrent macroscopic hematuria is self-limiting and requires no specific treatment.

Patients with persistent proteinuria (urine protein to creatinine ratio > 1, or lower if there is parental anxiety), even without hypertension, are also managed by angiotensin blockade with the addition of fish oil.

Patients with rapidly progressive deterioration of renal function, or patients in whom biopsy shows more than 20% crescents, are usually treated with three doses of intravenous methylprednisone followed by oral prednisone; fish oil and angiotensin blockade therapies may also be added once renal function stabilizes. If there is minimal or no response in 4–6 weeks, we would consider adding a second immunosuppressive agent. In the past, we have used either oral cyclophosphamide or azathioprine. More recently, we are using MMF instead at a dose of 600–1,200 mg/m^2/day in two divided doses. Patients presenting with nephrotic syndrome are treated with oral prednisone at 2 mg/kg/day with a maximum of 60 mg or 80 mg per day in pre- and post-pubertal children, respectively. This is then tapered once remission is achieved. If, after 4–6 weeks, no response is seen, additional immunosuppressants are added.

Clinically, the most challenging scenario is when a child has mild renal insufficiency and a moderate degree of proteinuria with or without hypertension. Although clinically mild, the patient is at risk of renal deterioration. We usually closely follow the patient in order to observe the patient for rapid renal function deterioration. If clinically stable with no sign of rapid renal progression, we usually start the patient on ACE inhibitor. If the patient has signs of renal progression, we recommend alternate day oral prednisone at 1 mg/kg for 6 months. If there is no improvement or rapid deterioration continues, we usually add an immunosuppressant.

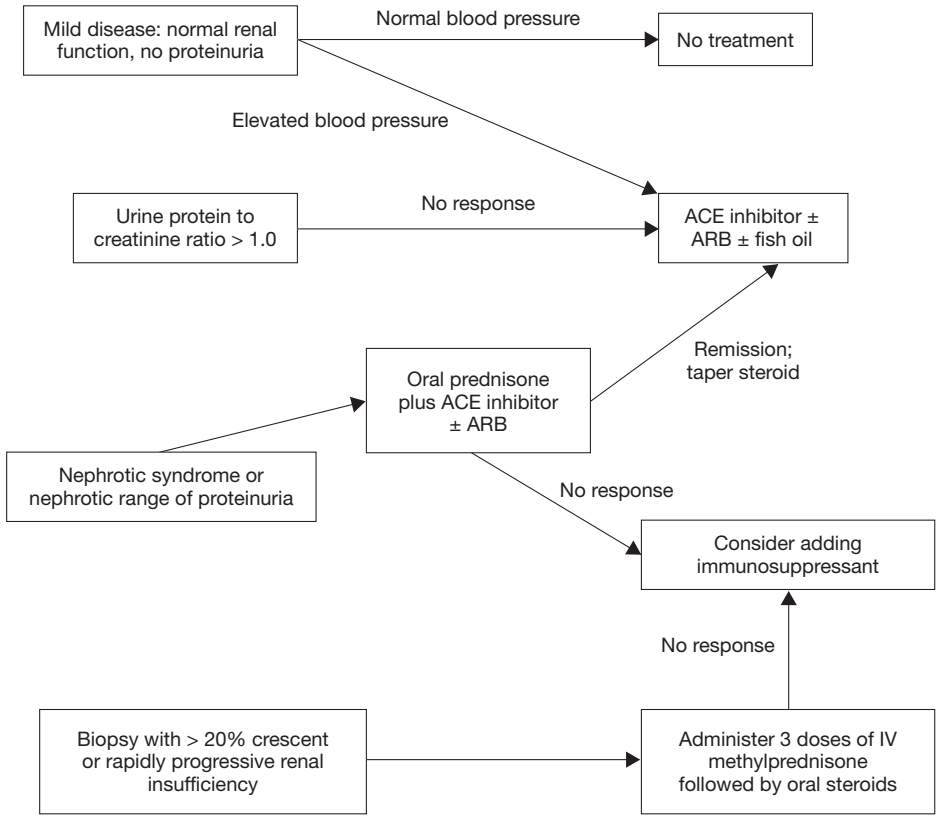

Figure. Approach to the treatment of pediatric patients with IgA nephropathy. ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; IV = intravenous.

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